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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,083	07/13/2001	Timothy I. O'Brien	D6223CIP/C/D	4623

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,083	O'BRIEN, TIMOTHY I.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26, 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 May 2005 has been entered.

2. Claims 1-25, 27-29 and 32-39 are cancelled.

Claims 26 and 31 have been amended.

3. Claims 26 and 30-31 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The rejection of claims 26 and 30-31 under 35 U.S.C. 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the invention was filed, had possession of the claimed invention (item no. 8 of the previous Office Action) is withdrawn in view of the amendments to the claims.

7. The rejection of claim 26 under 35 U.S.C., first paragraph, as failing to comply with the enablement requirement is withdrawn in view of the amendments to the claim.

8. The rejection of claims 26 and 30-31 under 35 U.S.C. 103(a) as being unpatentable over Paglia et al in view of Cohen et al is withdrawn in view of applicants arguments and amendments to the claims. In view of the new enablement rejection presented in this Office Action (see item no. 13 below), should applicant amend the claims to the native human SCCE polypeptide encoded by SEQ ID NO:30, this rejection may be reapplied as Cohen et al teach the complete sequence of the native human SCCE polypeptide, i.e., lacking its associated signal peptide and propolypeptide sequence.

9. The provisional rejection of claims 26 and 30-31 under the judicially created doctrine of obviousness-type double patenting over claim 6-11 of copending Application No.10/372,521 is withdrawn in view of the terminal disclaimer filed 5/13/2005, now accepted.

10. The rejection of claims 26 and 30-31 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting "amino acid sequence encoded by the DNA of SEQ ID NO:30" is withdrawn in view of the amendments applicants arguments and the newly submitted sequence listing filed 5/13/2005.

11. The rejection of claims 26 and 30-31 under 35 U.S.C. 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the invention was filed, had possession of the claimed invention (item no. 13 of the previous Office

Action) is withdrawn in view of amended sequence listing filed 5/13/2005, providing the correct DNA sequence encoding the full-length human SCCE protein as incorporated by reference in the originally filed specification at page 87, lines 2-7 and page 90, lines 1-6. Thus, no new matter has been added.

Response to Arguments

12. The rejection of claims 30-31 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained in part.

Applicant's response filed 5/13/2005 is found to be persuasive with respect to the SCCE fragments of any size and undefined structure, i.e., SCCE polypeptide that "has" the amino acid sequence of SEQ ID NO:31, 32, 33, 34, 35, 36, 80, 86 or 99 in view of the amendments to the claims.

Applicant's response filed 5/13/2005 is not found to be persuasive with respect to the claimed method of treating patients at risk of getting cancer. The response argues does not address the enablement of the presently claimed method of dendritic cell immunotherapy in patients at risk of getting cancer. Treating individuals and individuals "at risk of getting cancer" broadly encompasses preventing cancer. There is no teaching in the prior or post-filing art or in applicant's specification indicating that any cancer can be prevented, thus indicating the high degree of unpredictability of preventing cancer. In fact, treating individuals and individuals "at risk of getting cancer" would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a

normal cell into a cancerous cell including preventing genetic mutation, and immortalization.

Thus, the enablement rejection as it pertains to treating individuals and individuals "at risk of getting cancer" is maintained absent objective evidence to the contrary.

New Grounds of Rejections

13. Claims 26 and 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing activated T cells directed towards human stratum corneum chymotrytic enzyme (SCCE) comprising exposing isolated dendritic cells to the SCCE peptide consisting of SEQ ID NO:32 and exposing isolated dendritic cells to the mature human SCCE polypeptide encoded by SEQ ID NO:30 (i.e., lacking the signal peptide and propolypeptide) thereby producing activated dendritic cells and exposing said dendritic cells to isolated T cells wherein said activated dendritic cells present the SCCE peptide to said isolated T cells, thereby producing activated T cells directed towards said human SCCE, does not reasonably provide enablement for all embodiments embraced by the claims, i.e., reintroducing SCCE activated dendritic cells into an individual that has or is suspected of having or is at risk of getting (as discussed above) ovarian or prostate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claims, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims broadly encompass methods of immunotherapy targeted towards human SCCE in an individual comprising isolating dendritic cells from said individual, exposing the dendritic cells to the SCCE protein encoded by SEQ ID NO:30 or the SCCE peptide selected from SEQ ID NOS: 31, 32, 33, 34, 35, 36, 80, 86 and 99 and reintroducing said activated dendritic cells into said individual wherein the activated dendritic cells activate SCCE-specific immune responses in said individual, wherein the individual has cancer, is suspected of having cancer or is at risk of getting cancer, wherein the cancer is selected from ovarian or prostate cancer, which broadly encompasses preventing cancer (discussed above).

The specification discloses only the cDNA (SEQ ID NO:30) encoding the human SCCE, and SCCE peptides thereof of SEQ ID NOS:31, 32, 33, 34, 35, 36, 80, 86 and 99. The specification teaches that SCCE is frequently expressed in ovarian tumors (See Example 13, Tables 5 and 7) as detected by immunohistochemical staining and Northern blot analysis.

The declaration of inventor Timothy J. O'Brien filed 2/19/2003 submits that human SCCE 9-mer peptides corresponding to amino acid residues 5-13 and 123-131 of the human stratum corneum chymotrytic enzyme possess binding motifs of HLA class I molecules and were effective at inducing specific CD8+ CTL responses in vitro.

Based on the levels of human SCCE expression in ovarian tumor cells and the identification of amino acid residues 5-13 and 123-131 of human SCCE as HLA A2.1-binding motifs, applicant asserts that any SCCE protein encoded by SEQ ID NO:30 and the SCCE peptides consisting of SEQ ID NOS:31, 32, 33, 34, 35, 36, 80, 86 and 99 are useful for adaptive dendritic cell immunotherapy in individuals having or suspected of having or at risk of getting ovarian or prostate cancer. Neither the specification nor the declaration teach that the SCCE peptide consisting of SEQ ID NO:31, 34, 80 or 99 are binding motifs of HLA class I molecules and effective at inducing specific CD8+ CTL responses either in vitro or in vivo. The art of Hansson et al (The Journal of Biological Chemistry, 269(30):19420-19426, 1994, cited on PTO-892 mailed 11/12/04) teach the human SCCE polypeptide, which contains a signal peptide of 22 amino acids and a propolypeptide of 7 amino acids followed by the active enzyme (see Fig. 1A and page 19422, left column). Thus, the claimed SCCE peptides consisting of SEQ ID NOS:33, 35, 36 and 86, which reside in the signal peptide are not part of the active SCCE enzyme as the signal peptide is cleaved from the active native human SCCE, indicating the unpredictability as it pertains to in vivo immunotherapy directed against the SCCE signal peptide. Further, as discussed above the specification does not teach the specific parameters for selecting an individual that is at risk of getting cancer or for

preventing cancer. There is no teaching in the prior or post-filing art or in applicant's specification indicating that any cancer can be prevented, thus, indicating the high degree of unpredictability of preventing cancer. In fact, the claimed immunotherapeutic methods would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancerous cell including preventing genetic mutation, and immortalization.

The state of the art is such that Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells, known as MHC restriction. Only a minority of peptide fragments from a protein antigen are able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptide sizes of 12-15 residues are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I. These teachings indicate that many species for example, the species encompassed by the broad language of the instant claims, would not work. Wang et al (U.S. Patent 5,840,839, 11/24/1998) teach at column 19 that finding a peptide that binds to a MHC molecules and stimulates immune response is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that the structure of a T cell epitope that stimulates an immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate

T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs have to be tested experimentally in order to determine whether they are actually T cell epitopes or not. While it is known that size is a factor in processing and recognition of an epitope, it is also known that other factors are involved in T cell stimulation, all of which have not been elucidated. For support, see Bixler et al (U.S. patent 5,785,973, column 5, line 47 to column 7, line 59, cited on PTO-892 mailed 3/25/04). The art of Geysen (U.S. Patent 5,539,084, cited on PTO-892 mailed 3/25/04) shows that even for peptides of similar size derived from the same "parent" polypeptide, not all will be capable of interacting with T-cells (column 2, lines 5-9 and Figure 6), thus demonstrating the degree of uncertainty in the art for predicting which subsets or portions of a larger polypeptide will be capable of interacting with or stimulating T-cells. Neither the specification nor the prior art teach the full-scope of the SCCE proteins and the myriad of fragments thereof for activating T cells toward SCCE for immunotherapy in patients with a reasonable expectation of success.

One of skill in the art cannot extrapolate the teachings of the specification, which are limited to expressed in ovarian tumors (See Example 13, Tables 5 and 7) as detected by immunohistochemical staining and Northern blot analysis or the declaration of inventor Timothy J. O'Brien filed 2/19/2003, which submits that human SCCE contains two binding motifs of HLA class I molecules (i.e., amino acid residues 5-13 and 123-131 of the human SCCE), one of which is part of the signal peptide (i.e., residues

5-13 of human SCCE) and thus, not part of the active SCCE, and are effective at inducing specific CD8+ CTL responses in vitro to the full scope of the presently claimed methods because there is insufficient guidance or exemplification with respect to the SCCE peptides consisting of SEQ ID NOS:31, 33, 34, 35, 36, 80, 86 and 99 as well as the full-length SCCE polypeptide encoded by SEQ ID NO:30 for adaptive cellular immunotherapy in individuals. There is insufficient guidance regarding the parameters and specific cancer peptide sequences of SCCE, which correlate with the ability to stimulate T cells against SCCE in individuals commensurate in scope with the claims.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Hansson et al, Riott et al, Wang et al, Bixler et al and Geysen et al, the lack of established clinical protocols for effective cancer therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for adaptive immunotherapy in cancer patients, commensurate in scope with the claimed invention.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER